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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,228	11/14/2003	Luigi Grasso	MOR-0251	4529

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EXAMINER

CANELLA, KAREN A

ART UNIT	PAPER NUMBER
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1643

MAIL DATE	DELIVERY MODE
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02/08/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/714,228	Applicant(s) GRASSO ET AL.	
	Examiner Karen A. Canella	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 62-70,73-78,81-88,91-99,135 and 136 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) 62-70,73-78,81-88,91-99,135 and 136 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>7/18/07 + 12/10/07</u> | 6) <input type="checkbox"/> Other: ____ |

DETAILED ACTION

Claims 1-61, 71, 72, 79, 80, 89, 90, 100-134, 138 and 138 have been canceled. Claims 62-64, 66-70, 73-78, 81-83, 85-88 and 91-99 have been amended. Claims 62-70, 73-78, 81-88, 91-99, 135 and 136 are pending and under consideration.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The rejection of claims 62-70, 73-78, 81-88, 91-99, 135 and 136 are rejected under 35 U.S.C. 103(a) as being obvious over Borrebaeck (Adv Drug Delivery Reviews, 1988, Vol. 2, pp. 143-165) in view of Yelton et al (Journal of Immunology, 1995, Vol. 155, pp. 1994-2004), Zan et al (Immunity, 2001, Vol. 14, pp. 643-653) and Nicolaides et al (WO02/054856) is maintained..

Borrebaeck et al teach in vitro immunization and the production of hybridomas thereby (pages 145-146). Borrebaeck et al teach that high affinity antibodies are obtained only when low doses of antigens are used in vitro (pp. 150-151, under the heading of "Affinity"). Borrebaeck et al suggests that it would be useful to be able to obtain antibodies from in vitro immunization having affinities greater than 10^9 M^{-1} (page 151-151 under the heading of "Future Developments").

Yelton et al teach that increasing antibody affinity 10-fold provides a 2.5 to 3.0-fold therapeutic advantage in anti-tumor activities (page 2002, second column, lines 8-13 and lines 19-23). Yelton et al teach the cloning of hybridoma DNA into a cell expression system using codon based mutagenesis and the selection of higher affinity antibodies produced from the expression of the mutated hybridoma antibody genes (page 1995, Figure 1).

Zan et al (Immunity, 2001, Vol. 14, pp. 643-653) teach that B cell contain trans-lesion polymerases that include error prone polymerases (mis-pair inserters) and polymerases able to extend DNA chains from a mis-pair page 643, second column, second full paragraph to page 644, first column, line 22).

Nicolaides et al teach the use of chemical inhibitors of mis-match repair to make hypermutable cells. Nicolaides et al teach that the use of said chemical inhibitors is more efficient than relaying on natural mutation rates (abstract). Nicolaides et al teach chemical inhibitor of mismatch repair is an anthracene, ATPase inhibitor, nuclease inhibitor, RNA interference molecule, a polymerase inhibitor or an anti-sense oligonucleotide that specifically hybridizes to a nucleotide encoding a mis-match repair protein (page 10, lines 19-25). Nicolaides et al teach the cDNA encoding the mis-match repair proteins of SEQ ID NO: 14 (mouse PMS2), SEQ ID NO:16 (human PMS2), SEQ ID NO:18 (PMS1), SEQ ID NO:20 (MSH2), SEQ ID NO:22 (MLH1), SEQ ID NO:24 (hPMS2), SEQ ID NO:26 (GTBP) and SEQ ID NO:28 (MSH3) (pp. 40-66) which fulfill the specific limitations of claims 135 and 136. Nicolaides et al teach that an example of a host cell which can become hypermutable by treatment with the chemical inhibitors of the invention include human, mammalian and rodent cells (page 14, lines 1-3). Nicolaides et al teach the transient exposure of cells to the chemical inhibitor allowing for stabilization of the genome (page 10, lines 14-19) which fulfills the specific embodiment of claims requiring the stabilization of the genome.

It would have been prima facie obvious at the time the claimed invention was made to transiently expose hybridoma cells formed from in vitro immunized lymphocytes to chemical inhibitors of mis-match repair as taught by Nicolaides et al in order to mimic affinity maturation in vivo and obtain higher affinity antibodies and thus higher titer antibodies. One of skill in the art would have been motivated to do so by the teachings of both Borrebaeck et al and Yelton et al on the desirability of exploiting in vitro immunized antibodies to obtain high affinity antibodies; and the teachings of Nicolaides et al on the chemical inhibitors of mismatch repair for inducing cells including mammalian cells to become hypermutable and the teachings of Zan et al on the ability of B cells to induce somatic mutations therein by by-pass polymerases allowing for insertion of mutations and extension of DNA chains from the mutation. One of

skill in the art would understand that the inhibitors of Nicolaides et al would increase the rate of mutations inserted by the by-pass polymerases and thus provide for a higher rate of somatic mutations and the accumulation of a population of somatic mutants allowing for the selection of higher affinity antibodies formed as a result of said somatic mutation.

It would also have been obvious to clone the un-mutated genes from the hybridoma into a expression construct as taught by Yelton et al and expose said construct to chemical inhibitors of mismatch repair in place of codon-based mutagenesis. One of skill in the art would have been motivated to do so because the use of the chemical inhibitors is more efficient and less time consuming especially in the case of the anthracenes, thereby allowing for the screening of more hybridomas.

One of skill in the art would also have been motivated to select antibodies with an affinity of greater than 10^9 M^{-1} as taught by Borrebaeck et al and therefore fulfills the limitations of claims 69, 86 and 95.

Applicant argues that WO 02/054856 was, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person. This has been considered but fails to over come the instant rejection, because WO 02/054856 was published on July 18, 2002 and therefore qualifies as prior art under 102(a) as well as 102(e). Applicant will need to take action such as providing a Declaration under 131 in order to swear behind the filing date of WO 02/054856.

All other rejections and objections are withdrawn

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A. Canella/
Ph.D., Primary Examiner
Art Unit 1643